REMARKS

In the outstanding Office Action, claims 1 to 30 were presented for examination. Claims 3, 5 and 7 were rejected on formal grounds under 35 U.S.C. §112. In addition, rejection was advanced variously on the basis of 35 U.S.C. §102 or §103 against claims 1-30 as being anticipated by or unpatentable in view of references to Chang et al. and Olsen et al.

The Office Action has been most carefully studied. In this amendment, claims 3, 5, 7, 10, 20-22, 24, 27 and 29-30 have been amended. Claims 29 and 30 have been cancelled and new claims 31 and 32 have been added. The new and amended claims have been carefully written to avoid any questions under 35 U.S.C. §112, in accordance with the guidelines and requirements set forth in the outstanding Office Action. Accordingly, as will be discussed in detail below, it is believed that the application is clearly in condition for allowance.

Specification

Amendments have been made to overcome most of the informalities kindly pointed out by the Examiner. However, no amendment has been made to render "aminoacid" as two words. The compound form is believed to have acquired an accepted usage in the art as is demonstrated by a cursory electronic check of the Office's database which yielded the following results:

> **Results of Search in 1976 to present db for:**
> **aminoacid**: 2454 patents.

Given this extensive usage of the term, the burden on applicant and also on the Office of making this inconsequential change does not appear to be justified.

In addition the specification has been amended to replace the references to European patent applications and correct other minor informalities.

Claim Amendments

Claim 3 has been amended, without narrowing, to remove and question as to antecedent basis and to remove the minor typographical error therein. Claim 5 has been amended, without narrowing, or to make explicit language that was inherent, to positively introduce the respective numbers of charged amino acids. Regardless of the particular sequence of the recombinant gelatin-like protein it is believed that the requirement for a preponderance of at least 2 negatively charged amino acids appearing in claim 5, as now amended, is something which can be determined by one skilled in the art without undue experimentation. Claim 5 and also claim 20, have been amended in a manner which broadens and clarifies the claims by deleting the preferred option.

Claim 7 has been amended to overcome the rejection, by specifying the object or reference protein as being a natural collagen protein. Support for the amendment to claims 7 and 22 is inherent in the language of the respective claim before amendment and may be found in explicit form in applicant's specification at page 24, line 32 to page 25, line 7.

Claims 10, 24 and 27 have been amended, without narrowing, to correct minor informalities. Claims 15 and 28 have been amended, without narrowing, to add the subject matter of claims 29 and 30 respectively.

New claim 31 finds support on page 7 of the specification, at lines 12-25 and new claim 32 finds support at page 24, lines 23-30.

Claim Rejections - 35 U.S.C. §112 Indefiniteness

The rejections of claims 3, 5 and 7 are believed clearly overcome by the amendments made.

Claim Rejections - 35 U.S.C. §102(b) Anticipation

Turning now to the rejection of claims 1-4, 6, 9-12, 14, 18, 19, 24, 25 and 27 as anticipated by Chang, C et al., ("Chang et al.") claims 1-4, 6, 9-12, 14, 18, 19, 24, 25 and 27 are believed clearly distinguished from this reference or any other art known to applicant.

The Office points out that Chang discloses "a composition comprising recombinant gelatin having a molecular weight range of from about 0 to 50 kDa." This is true. The Office also states that Chang discloses a plasma expander comprising recombinant gelatin and a volume replacement material comprising recombinant gelatin. However, what little practical teaching Chang provides for realizing such applications teaches away from applicant's claimed invention. Specifically, Chang does not disclose a recombinant protein plasma expander meeting applicant's claim requirements that the recombinant protein have a molecular weight of from at least 10,000 Daltons to at most 50,000 Daltons and an isoelectric point of less than 8, as will be explained in more detail hereinbelow.

The Examiner also asserts that Chang et al. discloses "the ability to produce" recombinant gelatin with a desired isoelectric profile, pH, degree of hydroxylation and amino acid composition. A mere "ability to produce" various features is not a disclosure of a combination of features that will yield a desired result.

As is described in applicant's specification, in the paragraph bridging pages 1 and 2, Chang et al. disclose a great variety of recombinant gelatins and a great variety of uses of these recombinant gelatins. However Chang et al. does not disclose any specific structural feature of a recombinant gelatin that might render it useful as a plasma expander. Some general features that are supposedly important for use as a plasma expander are described at page 35 lines 29-37 of Chang et al. where it is stated that

> "A higher molecular weight, lower gel strength recombinant gelatin could be useful in various pharmaceutical applications...for example as a plasma expander."

The only gelatin feature that Chang et al. mentions as desirable for a plasma expander is that a partially-hydroxylated gelatin is suitable. Applicant's base claims 1, 2, 9 and 10 are believed clearly distinguished from, and therefore not anticipated by, these generalized disclosures of Chang et al. by the specific features of isoelectric point, molecular weight and freedom from crosslinking of the recombinant gelatin-like protein that are set forth in the claims.

Chang et al. is silent on what would be an appropriate isoelectric point for a recombinant gelatin to be suitable for use as a plasma substitute. Accordingly, Chang et al. clearly does not meet the requirement of base claims 1, 2, 9 and 10 that the recombinant gelatin-like protein suitable as a plasma substitute have an isoelectric point of less than 8.

Nor can a suitable isoelectric characteristic for use as a plasma substitute be inferred from Chang et al.'s sequence structure because no specific sequence feature is related to the proposed functionality of Chang et al.'s recombinant protein as a plasma expander. Furthermore, Chang et al.'s generalized remark at page 28, lines 28-38 regarding the ability of their methods to produce a recombinant gelatin with a desired isoelectric profile lacks any disclosure of what isoelectric profile would be suitable for a

plasma substitute. This being the only disclosure relied upon by the Office, or which applicant can find in the extensive specification of the reference, there can be no question, in applicant's view, that Chang et al. clearly does not meet applicant's claim requirement that a recombinant protein suitable as a plasma substitute to have an isoelectric point of less than 8. Accordingly, applicant's base claims 1, 2, 9 and 10 are clearly not anticipated by Chang et al., for this reason alone.

Nor does Chang et al. disclose a recombinant protein suitable as a plasma substitute which meets the requirement in applicant's base claims 1, 2, 9 and 10 that the molecular weight be at most 50,000 Daltons.

At page 32, lines 26-33, Chang et al. discloses that:

> "The molecular weight of a typical fibril-forming collagen molecule, such as type I collagen, is 300 kDa. In some applications, such as those in which high molecular weight gelatins are used, it might be desirable to produce a gelatin with a greater molecular weight than that of currently available extracted gelatin. Therefore, in one embodiment of the present invention, gelatin can be produced containing molecules larger than the collagen from which commercial gelatin is currently extracted. The resultant higher molecular weight gelatin product can be used directly in various applications in which its physical properties would be desirable, or can be divided and subsequently treated to produce molecules of a smaller sizes." *(Underlining added.)*

From this passage, Chang et al.'s higher molecular weight gelatin products may be understood to have a molecular weight exceeding 300 kDa, i.e. 300,000 Daltons. This higher molecular weight may be understood to be the same higher molecular weight as is possessed by the recombinant gelatin product referenced at page 35, lines 29-37 as being suitable for use as a plasma expander which disclosure is relied upon by the Office. Clearly, Chang et al.'s teaching as to what sort of recombinant gelatin product should be used as a plasma substitute is excluded by applicant's requirement in claim 1 that the recombinant gelatin product have a molecular weight which is "at most 50,000

Daltons". Even the tetramer protein defined in base claim 2 would have a molecular weight of at most 200,000 Daltons clearly excluding Chang et al.'s proposals for plasma expander proteins with molecular weights of 300,000 Daltons or more. Accordingly, claims 1, 2, 9 and 10 are believed still further clearly and patentably distinguished from Chang et al. or any other reference known to applicant, for this meaningful reason.

By way of even further distinction, applicant notes that Chang et al. fail to disclose the desirability that a recombinant gelatin product suitable as a plasma substitute should not be cross-linked by chemical modification, as is required by applicant's base claims 1, 2, 9 and 10.

Claim Rejections - 35 U.S.C. §103(a) Unpatentability

In the outstanding action, claims 1-30 are rejected as being unpatentable over WO 01/34646 (Chang et al.) in view of US 6,413,742 (Olsen et al.).

The Office cites Olsen et al. as disclosing a method that can be used "to make any fibrillar collagen as well as the corresponding types of gelatin for use in medical applications." and argues that one would have been motivated to use the recombinant method disclosed by Olsen et al. to produce a gelatin composition that would have no risk of contaminates such as bovine spongiform encephalopathy (BSE) or Creutzfeldt-Jakob disease.

It is not clear to applicant what Olsen et al. contributes beyond what is already disclosed in Chang et al. regarding recombinant gelatin-like proteins that might be employed in plasma substitute compositions. It is clear to one skilled in the art that when gelatins are produced in a recombinant manner there is no problem with contaminants relating to BSE and Creuzfeldt-Jacob disease. This is also known from Chang et al. Avoiding prion-induced contamination is not applicant's objective: it is an

inherent and beneficial property of employing a recombinant gelatin-like protein rather than a gelatin from natural sources, e.g. bovine gelatin.

As explained hereinabove, the primary reference, Chang et al. neither discloses nor suggests the meaningful combination of features required to be present in the recombinant collagen-like protein defined in applicant's base claims 1, 2, 9 and 10 to provide a plasma substitute, notably particular molecular weight and isoelectric point limits and the absence of chemical crosslinking. Olsen et al. does not remedy these deficiencies of Chang et al.. Nothing in Olsen et al. would assist one skilled in the art to determine what features of a recombinant gelatin protein might render the protein useful as a plasma substitute. Nor does the Office point to any disclosure in Olsen et al. which might be combined with Chang et al. to render applicant's claims unpatentable. Moreover, because Olsen et al. do not address the problems of providing a recombinant gelatin protein suitable as a plasma expander, one skilled in the art would have no reason to combine Olsen et al. with Chang et al.

Without admission, applicant speculates that the Examiner may have cited Olsen et al. for the use of the terms "trimeric collagen" and "collagen monomer" which are mentioned. It is noted however that the trimer and monomer of Olsen et al. refer to the collagen triple helix structure which is formed from three distinct collagenous proteins called monomers. Thus in the fibrillar collagens of Olsen et al. three separate proteins (collagen monomers) form a triple helix complex (a collagen trimer). In the presently claimed invention trimer (and also dimer and tetramer) refers to one protein comprising three (or two or four) repeats of a particular monomer sequence. Hence a trimer in the present invention is one distinct protein.

As Olsen et al. do not mention any characteristics for a recombinant gelatin-like protein that would make these particularly suited for use as a plasma substitute, it is believed furthermore clear that the claims are patentable over Chang et al. when

considered in combination with Olsen et al. or any other reference known to Summarizing, it is noted that neither Chang et al. nor Olsen et al. mentions or suggests the selection of the isoelectric point of a recombinant gelatin-like protein to be less than 8 for use in a plasma substitute composition. As is shown in Figures 2 and 3 of applicant's drawings, useful embodiments of the invention can provide an unexpectedly prolonged plasma volume expansion, or oncotic effect. It is surprising, and not remotely suggested by the art, that by selecting the isoelectric point to be less than 8, a relatively low molecular weight recombinant gelatin-like protein can be provided which has a valuable plasma expansion effect. Chang et al.'s only solution to the problem of providing a recombinant gelatin-like protein useful as a plasma substitute is to employ a molecular weight of 300 kDa or higher, which is not at all what applicant has claimed.

A further surprising and beneficial effect obtainable with certain embodiments of the invention, is that by employing multimers and monomers of the recombinant gelatin-like protein, such as are set forth in claim 2, in various proportions, it is possible to manipulate the duration of the oncotic effect as is described in applicant's specification, for example at page 24, lines 23-30.

Dependent claims

Dependent claims 3-8, and 10-30 are believed clearly and patentably distinguished from the art of record, or any other art known to applicant, for the reasons that the respective base claims 1, 2, 9 and 10 are believed patentable. Dependent claims 3-8, and 10-30 are believed furthermore patentable for the additional meaningful subject matter they recite.

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for

allowance. Such action is most earnestly solicited. If for any reason the Examiner feels that consultation with Applicant's representative would be helpful in the advancement of the prosecution, they are invited to call the telephone number below for an interview.

Respectfully submitted,

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